GCP Considerations

Study AC-060A202: CONTROL

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ACTELION

What is Study Quality?

Measure of conformance of a clinical study to certain specifications or standards, such as

- Local Regulations
- Good Clinical Practice
- Ethical Standards
- Data Protection

ICH GCP 1990…

- Protecting Research Subjects
- Ensuring the quality and integrity of research data for regulatory decision-making
- Assuring the existence and operation of “quality systems”

The Principles of ICH GCP (ICH E6 2)

1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
3	The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society
4	The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion
7	The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist

The Principles of ICH GCP (ICH E6 2)

8	Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks
9	Freely given informed consent should be obtained from every subject prior to clinical trial participation
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements
12	Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented

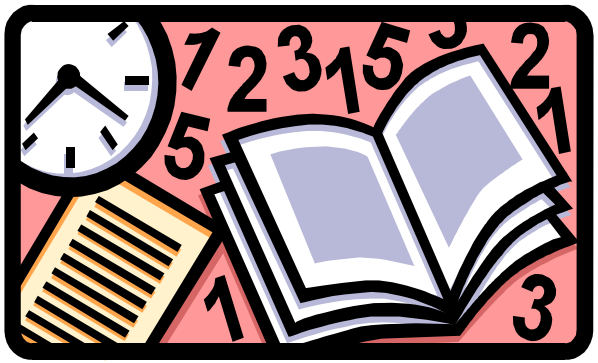
Protecting Research Subjects - Informed Consent

- Voluntary and documented confirmation of a subject's willingness to participate in a trial
- The right to say "NO"
- Information provided verbally and in written
- Uncomplicated, in subject`s understandable language
- No participation or withdrawal from the study will involve no loss of benefits or rights of care
- Withdrawal at any time during study possible

NOT JUST A SIGNATURE ON A FORM

Process of obtaining IC: When to be signed?

- After
  - subject received adequate information
  - had ample time to read it
  - all questions were answered



- **Before**
  - any trial-related activity

  -date and TIME need to be handwritten by patient

- Continuing throughout trial

Records and Documentation:

- **GCP perspective:**

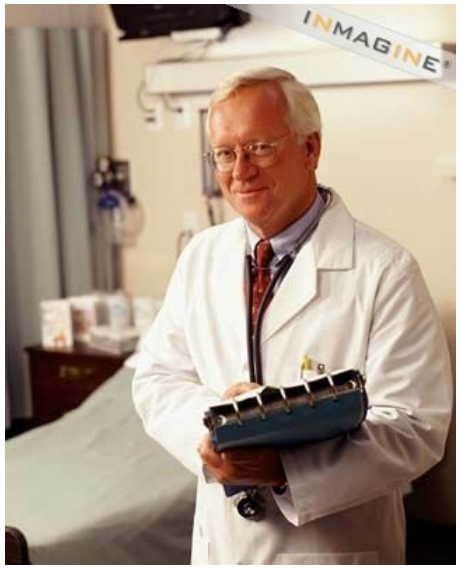
<u>What is not documented, does not exist!</u>

- **<u>Active</u> vs passive recording**

A short note makes the difference!

Documenting the IC process

- A properly completed and signed consent form serves to document the consent process
- To be personally signed and dated by the subject and the person obtaining consent
- A note in the chart helps to support the process
  - The study ID
  - Statement by whom subject was informed
  - Date and time of the consent
  - Confirmation that subject received a copy of the signed consent form



Informed Consent– Some typical critical / significant findings

- Consent process not verifiable
- All signatures dated/timed by one person or time/date missing
- Physician's involvement not verifiable
- Physician dated/timed for subjects
- Handling of blood samples not done in accordance with ICF (more blood taken)
- PI not aware of contraception methods/reproduction risks

Study Personnel - Delegation of Authority
ICH GCP Sec. 4.1.5

- PI to confirm (sign and date) the authorization of assigned tasks and of the appropriate training received by each site personnel
- PI authorization of personnel before study involvement
- Without authorization by PI on DoA, no tasks to be executed
- Tasks must be delegated according to the qualification's level of site personnel
- DoA to be consistent with training completion log

Study Training - Training Attendees Record
ICH GCP Sec. 4.2.4

- Training of site staff to be documented
- Training status of team members has to be clear and consistent with follow-up letters

Drug Supply – ICH GCP Sec. 4.6

Study drug management:

- Patients to return all unused study drug (even empty blisters) at each visit!
- Records to be kept about:
  - Drug dispensed
  - Drug used
  - Dosages administered
  - Drug returned

Drug accountability is more than just pill-counting!

- Drug accountability to be performed on an ongoing basis until completion of study

Drug Supply – ICH GCP Sec. 4.6

- Administration of drug as per protocol
- IMP accountability to be documented on the IMP Dispensing and Accountability Log
- Prescriptions for study drug administration and temporary or permanent discontinuation to be signed by study physicians
- Personnel responsible of IMP prescription, dispensing, IMP accountability must be listed on the DoA

Source Documents – ICH GCP Sec. 4.9 Availability and Completeness

- ECGs, Laboratory Reports, Spirometry reports
  - To be medically assessed, signed, dated
  - In a timely manner, not batch-wise
- Ensure complete information on Screening/Randomization form
- Process of consenting and/or re-consenting
- Medical assessment of AE
- Result of pregnancy

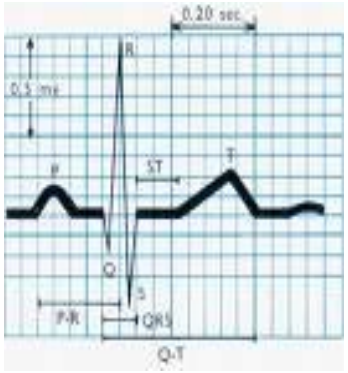
WHAT IS NOT DOCUMENTED, DOES NOT EXIST

Source Documents - Availability and Completeness

Typical findings

- Language proficiency not verifiable (subject Hispanic, signed English consent form)
- Physician's order for start/stop/discontinuation of study drug not verifiable
- Printouts from EMR records not stapled together, signed and dated
- EMR hospital system not assessed properly if compliant with 21 CFR requirements
- PI's involvement in decision to take subjects study not documented
- Changes of critical data in SD not signed and initialled

Safety Monitoring

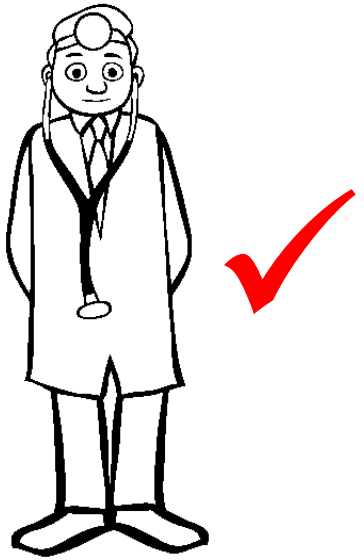


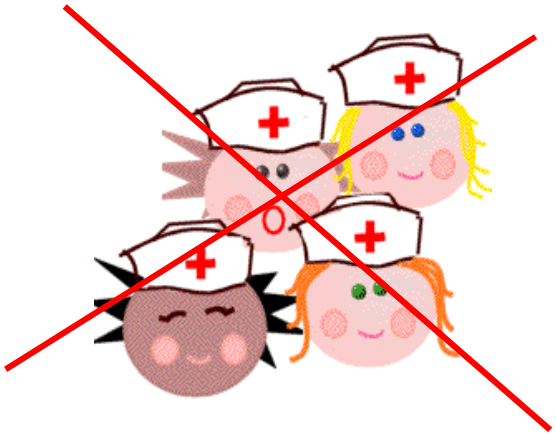
Safety data

- To be recorded in source
  - Active – if NO AE, document this fact!
  - AE – the minimum to document are diagnosis, treatment, start date, end date, any further medically relevant issues
- Adequate documentation of safety monitoring activities, e.g. initializing and dating of laboratory reports, ECG-reports ...

Safety Reporting- ICH GCP Sec. 4.11

- Ensure submission of SAE to Actelion in accordance with the protocol
- Respond to Global Drug Safety query asap
- Medical assessment has to be done by physician





Protocol Compliance – ICH GCP Sec. 4.5

Protocol Violations – Some typical examples

- Protocol related procedures not done
- Drug administration not stopped as per protocol
- Pregnancy tests not performed per protocol, adherence to contraception use not followed
- Study specific procedure performed prior consent
- Persistent recurrence of same violations despite adequate staff retraining may lead to a potential serious breach

NO WAIVERS WILL BE GRANTED

How does Actelion structure Audit outcomes?

Judgment / Categorization of Severity

Critical

Violations of critical ethical and/or regulatory provisions and/or major inadequacies in the data quality were observed which could lead to any or all of the following: rejection of the data if inspections were to occur, impact on the patients safety, legal or ethical rights, result in regulatory action or have a major media impact.

How does Actelion structure Audit outcomes?

Judgment / Categorization of Severity

Significant

Does not jeopardize the acceptability of the study but is a violation of GCP and/or internal SOPs, and/or local regulations

On-site Investigator Audits

- To have someone independent to review the study conduct
- To look at something from a different perspective

Thank you!